Reprinted from the BRITISH MEDICAL JOURNAL, *July 27th, 1912.*

THE RELATIONS OF THE CIRCULATION.

Address in Medicine delivered at the Eightieth Annual Meeting of the British Medical Association.

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THE honour of delivering the Address in Medicine, which, by the grace of the Council, has fallen to my lot, is the highest distinction, in my judgement, at the disposal of that body. My grateful appreciation of the favour shown to me is attended by the reflection that no privilege can be divested of responsibility; it is my duty to turn this opportunity to a useful purpose, so far as lies in my power. As most of my life work has lain in the observation and investigation of the circulation, it is only to be expected that in a consideration of the problems it presents lies my best hope of practical utility. Another strong influence draws me also in the same direction. Six years ago, at our meeting in Canada, you, Sir, when occupying the position now accorded to me, chose for your subject: "The Circulation viewed from the Periphery." Many problems arising out of your suggestive remarks forced themselves upon my mind while listening to your words—problems mostly concerning the manner in which the circulation is brought into relation with the body at large—and to-day it seems fitting, while you preside over us, to make an effort to answer some of the questions springing from your statements and still claiming our attention.

It is possible—nay, even probable—that such an attempt may seem too ambitious; the subject is at once so extensive and so elusive. In the hope, nevertheless, that good may somehow come from honest inquiry, and with the assurance, moreover, that any shortcomings will be leniently judged, my desire is to lead you with me to some of the intricate and perplexing paths in the field of modern medicine. If the pursuit of science be indeed, as we believe it to be, a pilgrimage in quest of truth, it is manifestly incumbent on us to discover what is its nature and where it is enshrined. Modern physiology had its birth in the central

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facts of the circulation, and numerous researches on that subject during our own epoch—the age of scientific medicine—have given abundant proof of earnestness in the search.

In considering some of the recent additions to our knowledge, whether gained in the hospital or in the laboratory, it is more than likely that many of the thoughts about to unfold themselves will be to my hearers in no sense novel. Certain are, indeed, current coin; all have for some years been in the air. A certain amount of hesitation in advancing ideas which seem to reflect upon ourselves a flavour of originality is only natural; most of us tremble lest we fall into the ranks of those who, by regarding the "stepping stones of their dead selves" as rocks upon which others are still reposing, become the victims of self-complacency.

The complex mechanism by which the balance of the circulation is maintained has, during the whole modern period, been the subject of untiring research. The student has not been contented with fleeting phantoms, like "a dream within a dream"; he has yearned after facts and has longed to reach down to the bedrock of certainty. Amongst the objects which have aroused the patient enthusiasm of the worker, the connexions between the central and peripheral divisions of the cardio-vascular system, and the relations between the whole of that system and the body at large, have furnished objects of investigation absorbing his energies. In recent years a wealth of reward has been vouchsafed to him.

Nature is not ungenerous. She does not hide herself with the veil of Isis; she is ever willing to reveal her secrets to the humble suitor. Some of the appearances she presents may not be clear at first, but in time their hidden meaning is grasped. The end of the quest can never be gained by incantation; only by dint of patient and ceaseless effort is the goal won. Without facts, often gathered with painful effort, all our arguments are in vain. Do you remember the tradition of Pietro di Medici, unworthy successor of Lorenzo the Magnificent, who ordered Michael Angelo to fashion a statue of snow? The story has aroused the scornful contempt of four centuries, and may be traced in the burning words of Mrs. Browning and Mr. Ruskin. In similar fashion, the man of science who is asked to devote his mind to discussion without permanent truths wherewith to reason, is in the same position as the great sculptor, when he was commanded to carve a figure out of melting material.

The part played by the circulation in the integration of the organism is a natural subject for our thoughts in this city, where the author of the fascinating Silliman Lectures presides over the domain of physiology. The subject must be admitted to be a very large one, as it does not only include the consideration of the connexions of the central and the peripheral portions of the cardio-vascular system, but, as already suggested, the relations of the circulation as a whole to the body at large. It comprises the nature of the actions and reactions continually in operation, and the character of the stimuli and responses likewise constantly at work.

The circulation in all the higher animals may be regarded as based upon, or concerned with, four primary groups of principles. It is based upon mechanical arrangements which form the foundation for all its operations. It requires chemical changes, by which it is maintained, and for which it provides possibilities, by transference of matter. It is modified by glandular secretions, which profoundly alter its mechanism and chemical processes. It is affected by nervous agencies which deeply influence the performance of its functions.

When we gaze upon the long line of being through which the mammal has been evolved we can discern certain different stages of development, physiological no less than morphological. Amongst the simple organisms belonging to the protozoa, physical and chemical agencies alone are required—simple structure and function are alone brought into play; amongst the complex beings constituting the metazoa, glandular and nervous influences make their appearance with ever-increasing complexity—as we arise in the scale of life elaborate structure and function are necessary.

To which part of the masque of life shall we wend our way in search of observations with which to illustrate the subject? Whithersoever we turn our eyes we can see but a small part of the drama at once. We do not yet stand "upon a Peak in Darien." We can find examples of our meaning in the growth of youth and the decline of age, in conditions of health and states of illness. We shall have occasion, in looking into certain processes which are to occupy our attention, to trace out the development of nervous and glandular agencies in their evolution as well as involution; and it will be necessary for us also to glance briefly in passing at some particular diseases which will be helpful in lighting the path of inquiry.

Many stages of being in the evolution of the mammal are analogous to phases of life in the development of its individual representatives. The analogies involve structure as well as function. In the newly born there is not merely disproportion in the size of different parts and organs as compared with the adult, but there is also difference as regards function. It would serve no useful purpose on this occasion to dwell particularly on the infantile divergences from the normal of adult life as regards size and weight; but it is of importance to linger over certain deviations in function. The heart of the baby, in relation to the weight of its body, is considerably larger—expressed in percentages of total weight it is almost 0.9, as compared with a little over 0.5 in the adult—almost double; even more striking is the fact that the frequency of the heart beat is much greater, being from 130 to 140 per minute—roughly speaking, double that of the adult; the whole circuit of the blood is therefore traversed in a much shorter time—rather more than onehalf. It therefore follows that the blood is renewed in the tissues of the baby with greater rapidity than in the adult. The total amount of blood, as compared with body weight, is considerably larger in the baby than in the adult; and as the respiratory work, although increasing absolutely with the growth of the body, is nevertheless relatively greater in early life, the absorption of oxygen is much more active than the production of carbonic acid. Metabolism, as the result, is extremely active within a few days of birth.

The glandular system soon after birth shows some interesting contrasts to the normal of the adult. The lymphatic system is extremely prominent, and the lymph circulation remarkably active. The thymus body increases in size up to the second year; from which point, as a rule, it undergoes retrogressive changes. The thyroid gland is larger in the baby than in the adult; while, on the other hand, the spleen is slightly smaller. This is what might *a priori* be expected; anabolism is in excess of katabolism. The glands which yield an external secretion show variable activities in the baby. The saliva, for example, is very scanty until dentition begins; it is also less active in the digestion of starch than is the case in the adult; on the contrary, the gastric secretion has adequate peptic powers; the pancreatic secretion has active tryptic functions, although the amylolytic power is feeble.

The first epoch of life is marked by the onset of dentition; and it may be held that, until the permanent teeth are nearly complete, this epoch is still existent. During it the infant passes through childhood into adolescence. Soon after the practical termination of the permanent dentition another great epoch of life takes place, and with it a new phase of activity sets in. This is conditioned by the development of the reproductive organs, and results in sexual differentiation, hitherto potential, but now functional. Although "The Salique Law of Nature" shows itself from the earliest period, even at birth, yet the differences between the sexes, especially in respect of external characters, occur in relation to the advent of reproductive possibilities.

From the commencement of this epoch until the end of maturity and the commencement of decline, the changes are so slight as to be almost imperceptible; but in the fifth decennium, in most persons of either sex, alterations both in structure and function become obvious. The general outcome of those changes may be stated in broad terms as a tendency on the part of both sexes towards each other; in other words, there is an approximation in each to a common type. It cannot be doubted that the divergences from such a common type during adolescence, and the return towards it during senescence, are determined by the functional activity of the reproductive glands; the recent work of Geddes and Marshall, although on different lines, gives clear evidence of this fact.

As old age advances, along with a gradual weakening of the muscular and nervous apparatus, there are at once external and internal changes of the most interesting kind, and the metabolic activity of the body, which in youth not only balanced the daily waste, but added new material, and in adult life was sufficient to meet the demands with ease, becomes so impaired as to be unable to sustain the frame entirely. It is probable that every tissue in the body participates in these retrogressive metamorphoses, but there can be no doubt that the glands, heart, and vessels play the most important part. In the shrinking of the skin, the loss of its appendages, the tendency to calcareous and fatty degenerations, we see the effects of such changes, and about the tenth lustrum certain degrees of a myxoedematous tendency are extremely common. From this point the changes follow with increasing rapidity, until there ensues the final phase, so beautifully decribed by the Hebrew preacher and the Roman poet.

How growth, equilibrium, and decline are related to the circulatory, glandular, and nervous systems, some attempt at explanation will, in the following remarks, be made. The disturbances of the normal processes by the incidence of disease, whereby new chemical and biological problems are involved, will also receive our consideration.

Let me carry you now in thought, before entering upon the glandular mechanism, to some examples of the wonderful nervous influences which preside over the heart and vessels, linking them up with the rest of the body. The whole life of an animal, according to Starling, " may be looked upon as a series of reflex actions." Nowhere is this more obvious than in the relations existing between the nervous and the circulatory apparatus. Of this fact a few simple illustrations may be cited. The idea of profound disorders of circulatory relations through vasomotor disturbances has been gradually growing up since the discovery of the nervous connexions controlling the circulation. The observations of Landois on the reflex origin of anginous pain, and of Nothnagel on its connexion with vasomotor contraction, as well as the more recent work of Pal on vascular crises, furnish sufficient evidence of this proposition. The receptive field, as Sherrington shows, presents a remarkable contrast between the afferent tracts of the somatic and splanchnic realms ; there is a wonderful richness in receptors of the former, or exteroceptive, as compared with the remarkable poverty of the latter, or interoceptive field. Mackenzie and Head have taught us how splanchnic impulses reaching the receptive and perceptive centres are referred by them, as the result of their development, to the somatic area. Nowhere is this truth more clearly manifested than in the various degrees of cardiac pain.

Since the early researches of our countryman, Lower, into the nature and cause of dropsy, the matter has been the preoccupation of many an anxious inquirer. One of the first steps in our modern knowledge of this important subject was the discovery by Ranvier that stasis in a limb is followed much more certainly and much more quickly by oedema if the nervous influence of the part be withdrawn. The close association of oedema and glossiness of the skin with neuritis is now universally known, and is of analogous nature. One of the most important contributions within recent years is that of Ninian Bruce, who has shown that the initial dilatation of the vessels in the early stages of inflammation depends upon the influence of the local nerves, and that it probably is of the nature of an axon reflex.

The heart and the vessels are subject to direct and reflex influences, now generally recognized as entering by every channel and flowing from every part of the body. The effects of emotion, such as joy and grief, pleasure and pain, rage and fear, are exerted directly through the action of the upper centres upon the lower. The majority of nervous influences, however, are reflex in their nature. Some of these are restricted in their localization—the receptor, the conductor, the effector consisting in the different parts of a single neurone. Such are obviously the alterations which take place in a local hyperaemia. Between a simple vasomotor reflex like this, on the one hand, and such profound and extensive disturbances as may give the widespread changes of angina pectoris, there is no abrupt transition—simply a complete chain of many links. Let me cite two recently described reflex arrangements. One of the most interesting of these reflex influences is that which we may hold as proved by Stewart in the case of aortic incompetence. The series of brilliant observations upon which he has based his theory has rendered it beyond doubt. Another admirable example of reflex influences recently studied is that suggested by Hill to explain the now generally recognized alteration in the relative arterial pressure of the arm and leg in the same disease. The arterial pressure is normally higher in the leg than in the arm, but the difference of pressure in health is very far exceeded by that which occurs in aortic regurgitation, and for this Hill has suggested that the arterioles of the leg undergo reflex contraction in order to preserve the balance of pressure in the centres at the base of the brain.

The instructive experiments of Cushing, carried out by introducing fluid into the cranial cavity, have taught us, in the most convincing manner, how intimate is the relation between cerebral compression and arterial pressure. Increased intracranial pressure in its advanced stages produces cerebral anaemia, and the centres in the medulla oblongata respond, as is necessary for their very existence, to the stimulus created by want of blood. The vasomotor centre raises the arterial pressure to overcome the compression of the centres, and at the same time the vagus centre is excited, so that the pulse-rate becomes reduced. It is not too much to say that by these valuable investigations Cushing has not only greatly widened our scientific knowledge, but has also profoundly modified our practical management of cerebral diseases. A passing reference may be permitted to the remarkable work of Crile on the state of the circulation, especially of the arterial pressure, in shock, from which we have learnt much. The recent investigations of Gray and Parsons have also assisted greatly in the elucidation of this subject.

Hitherto there has been a tendency to regard the vessels of the heart and the lungs as beyond the influence of the vasomotor system. Until lately, little experimental evidence has been obtained of any vasomotor mechanism in the pulmonary and coronary arteries. The recent investigations of Argyll Campbell, however, show that in the case of both systems the administration of pituitary extract by perfusion causes marked and prolonged constriction. This contraction is by the physiologists regarded as evidence in favour of vasomotor innervation of the arteries. More recently, Brodie and Cullis have proved beyond all possibility of doubt that the coronary arteries have both vaso-constrictor and vaso-dilator nerves, both being derived from the sympathetic system; the former are, as would be expected, the more powerful.

If we desire an instance in which to find an example of the intimate connexion between circulatory and glandular changes, we have not far to seek—it is always to our hand in Graves's disease. Just as in the case of glycosuria, we find hereditary, neurotic, and traumatic factors at work; its invariable association with glandular and circulatory changes, moreover, has long been known. In exophthalmic goître there are symptoms connected with the digestive system due to catarrhal and hyperaemic conditions; of the glandular system in thyroid enlargement, and less frequent alterations in the thymus, the pituitary, the suprarenal, and the lymphatic glands, as well as the spleen; the blood often reveals the presence of anaemia and, less commonly, of cyanosis, while varying degrees and types of leucocytosis are not infrequently encountered; the circulation does not merely reveal the presence of increased frequency of pulse-rate, but of very varying degrees of arterial pressure, while the heart may manifest considerable dilatation, with or without hypertrophy; the renal conditions may be largely modified, not only by the existence of polyuria, but of albuminuria or of glycosuria; the integumentary system may be the seat of the most multiform rashes, and also of atrophic changes particularly affecting the cutaneous appendages; in the nervous system are to be found remarkable divergences from normal conditions—sensibility diminished, perverted, or increased, motility usually affected in the direction of irritable weakness, with exaggeration of the reflexes and responses, diminution of muscular energy, shown by weakness of the movements and tremulousness of the muscles and disturbances of the delicate processes of co-ordination especially as regards the eye, vasomotor and visceral changes, and, above all, profound alterations in the higher cerebral functions—such are the outstanding features of the affection. It will certainly be useful to look further into certain matters connected with this interesting disease. A few instances of emotional causes may be given.

Debove tells us of a sailor, who fell into the sea at Marseilles, and thought he was about to be drowned. Almost before he was out of the water he began to show symptoms of Graves's disease. Cléret mentions an instance produced by the sudden and tragic death of a husband. In my own experience similar cases have not been infrequent. A lamplighter, after Saturday evening libations to one of his gods, in whose worship he showed zeal worthy of a better cause, did not wake up sufficiently early on a bright Sunday morning to be on his beat at the appointed hour. Living two miles from the scene of his labours, he ran the whole distance, and then proceeded, in the old fashioned method, to put his lamps out, by using a ladder for each. On the Monday morning he presented himself before me at hospital as an out-patient, and already symptoms of exophthalmic goître were evident. A washerwoman, while standing at her tub, received a great fright by the roof of her house falling in upon her, and she entered my ward two or three days later with pronounced features of Graves's disease. Traumatic instances are frequent. Delorme, for example, tells us of two officers who on parade fell from their horses on to their heads, and shortly afterwards were victims of the disease. Many reflex causes for the affection have been found. Irritation connected with the mucous membrane of the digestive, respiratory, renal, and reproductive systems plays an undoubted part in causation; when these conditions are relieved, the affection is greatly ameliorated. Are we to regard such emotional traumatic and reflex cases as certainly due to purely nervous causes? By no means.

The facts showing the causal nexus between the thyroid gland and Graves's disease have, in recent years, greatly accumulated. There is not merely the almost constant association of thyroid enlargement with the disease, but there are the further facts that it sometimes follows simple bronchocele, and not infrequently precedes myxoedema. The experimental production of symptoms closely resembling, if not indeed absolutely identical with, Graves's disease in different mammals, and the aggravation of symptoms produced by the administration of thyroid extract, through misdirected zeal, help us greatly in understanding the connexion.

It has long been known that the thymus gland undergoes revivescence in Graves's disease, sometimes adding greatly to the danger of surgical intervention. Some new light has been thrown upon this subject by the investigations of Bircher. He implanted fresh thymus gland into five dogs, and found very definite results. Within twenty-four hours there was excitement and thirst; in three days there was distinct tachycardia; by the fifth day exophthalmos was present; within twenty-eight days there was obvious goître.

Even the ardent supporter of the nervous origin of the disease admits that, although the structural lesion or the functional disturbance of the thyroid gland is not the cause of all the symptoms, it must be recognized that it plays an important part in the genesis of a great many of them. On the other hand, the keen adherent of a purely glandular cause for the disease is forced to admit that many of the symptoms of the disease, while primarily due to thyroid activity, must be brought about by the intervention of the sympathetic system.

The greatest outflow of the sympathetic fibres from the cord, as has been shown by the investigations of Gaskell and Langley, corresponds remarkably with the position of the greatest number of cells in the intermedio-lateral tract. The intermedio-lateral tract is found at three levels of the spinal cord—the upper cervical; the lower cervical, dorsal and upper lumbar; and the lower sacral region—one of the finest, as it was, alas! one of the latest, contributions made to neurology by Alexander Bruce, showed definite lesions in this tract. Changes in nervous structure have often been described before—neuritis of the cervical sympathetic by several observers; haemorrhage into the floor of the fourth ventricle by Cheadle and Hale White; bulbar haemorrhage with the formation of colloid bodies by Grainger Stewart and myself, as well as many obviously accidental lesions. But it is my pleasant duty to state clearly that the labours of Bruce have thrown a new light on the subject. In a case of the disease he found capillary haemorrhage in the lateral columns of the second, third, and fourth thoracic segments of the cord, with degeneration of the cells of the intermedio-lateral tract of these segments. Now, as Langley has shown, dilatation of the pupil, protrusion of the eyeball, and acceleration of the heart, are produced by stimulating the sympathetic roots of these segments.

The question of causation seems to many observers associated with the rapidity of development. Such instances as those mentioned above, in which the onset was dramatic in its suddenness, have often been considered as too swift in genesis for aught but a nervous cause. The celerity with which analogous symptoms were developed in dogs after the experiments of Bircher has given us new views on this matter.

In almost every respect the group of affections, for the explanation of which our thanks are due to the perspicacity of Gull, stands in direct antithesis to Graves's disease. In the various forms of myxoedema, no matter how produced, we have a group of diseases contrasting most markedly with exophthalmic goître. While the digestion and the blood may show changes somewhat analogous to those referred to in Graves's disease, there is, on the whole, less tendency to leucocytosis and anaemia. The circulatory symptoms are entirely different, as diminution of the pulse-rate and elevation of the arterial pressure are usually found, and although the heart is often hypertrophic, it has less tendency towards dilatation. Polyuria, albuminuria, and glycosuria may be found in both; but the condition of the skin and subcutaneous textures is distinctly contrasted in the two affections, except in respect of some loss of hair, and even nails, in some cases of Graves's disease. The increased bulk of the subcutaneous tissues, and the singular alteration in consistence exhibited by them, are characteristic points of divergence, while the striking alteration in appearance, resulting in the stolid, squat aspect of myxoedema, as contrasted with the alert and slender appearance of Graves's disease, is most marked. When we enter upon a comparison of the nervous conditions in these two diseases we are quite as much impressed. Instead of the eager nature, and neurotic features of Graves's disease, we have an apathetic character with lethargic appearances in myxoedema.

Thanks to the labours of numerous inquirers, amongst whom Murray especially deserves our grateful acknowledgements, we now have a firm foundation of knowledge for our discussion of the disease. We recognize that in some way it is intimately associated with the condition of the thyroid gland; the exact relations will appear in the sequel. It is clearly understood that the myxoedematous symptoms are dependent upon deficient thyroid activity, which may be the result of arrest of development, occurrence of disease, or surgical adventure.

Ever since the description of acromegaly by Marie, this singular affection has had a remarkable fascination for my mind. The enlargement of the head and extremities—particularly of the lower part of the face, the hands, and the feet; the marvellous adaptations whereby the increased weight of the head is compensated for by a decided hypertrophy of the cervical vertebrae, and that of the lower jaw by a remarkable enlargement of the temporal fossa and ridge; the strange alterations in structure of the internal viscera, which have recently been so thoroughly studied by Geddes; and the striking alterations in the field of vision, even now occupying the attention of Evans and Traquair, have invested this disease with a halo of interest which, notwithstanding the uncouth appearance of the victim, may almost be termed that of romance. When we further consider the most interesting suggestion of the lamented Cunningham, now abundantly verified, that gigantism and acromegaly are the same disease, as it affects early years, before the union of the epiphyses and diaphyses, or adult life, when ossification is complete, we are led to regard the condition as remarkable. We may assume without fear of contradiction that acromegaly is connected with alterations, either structural or functional, in the pituitary body; the exact relation of these to the affection will be subsequently dealt with. In an address given by me to the Medical Society of London some years ago, the processes of adaptation and compensation shown by this interesting disease were fully dealt with; and in a previous address to the Medico-Chirurgical Society of Norwich, the speculation was thrown out that probably the pituitary body would be found to exert an action upon other glands concerned in growth—further, that certain cells of the gland might be assumed to preside over particular parts of the body. In no other way does it seem to me possible to explain some of the extraordinary cases of local hypertrophy of extremities, which must be regarded as partial gigantism, or localized acromegaly.

The exact method by which the pituitary body regulates growth is still unknown. We shall in a few minutes review the relations between the structure and the function of the gland. In this place it must be allowed that we do not know how it acts. Whether it exerts its influence directly through the vessels, or by means of the vessels and their nerves, or through a power of stimulating or inhibiting other glands, is yet unknown. My own belief has always been that its main effect is a power of stimulating other glands to activity. In this way it seems possible to account for the great strength attendant upon the excessive growth commonly seen in the early phases and for the profound weakness invariably found in its later stages. The very interesting autobiographical sketch by Leonard Mark repeats the experiences, as regards this aspect of the disease, of every one of us who has ever seriously applied himself to the study of the disease.

Another most interesting affection, in which the glandular apparatus participates—may, indeed, be said to play a predominant part—is Addisonism. Ever since the discovery by Addison of the constant relations between pigmentation of the skin, weakness of the circulation, and disturbance of the digestion and morbid changes in the suprarenal glands, this condition has been universally recognized. It is, however, only in our own times that we have learnt in what respect the obvious symptoms are related to the glandular alterations. We now know that, when the usual fibro-caseous changes occur in the whole suprarenal gland, involving its medullary, as well as its cortical portion, there is a complete picture of Addison's disease, with discoloration, low arterial pressure, feeble heart impulse and weak cardiac sounds, digestive disorders, and profound asthenia, showing the three important groups of symptoms. But we are now sufficiently conversant with the affection to know that if there be an alteration of the cortical portion alone, there will be pigmentation only, with little or no change as regards the digestive, circulatory, or nervous systems. That, on the contrary, when the medullary portion is alone involved, there will be great reduction of arterial pressure, attended by loss of tonicity and contractility of the heart, the result of which is profound asthenia.

The opportunities afforded by our new research laboratory in connexion with the medical wards of the Royal Infirmary have enabled us to obtain a very considerable number of electro-cardiograms in exophthalmic goître, myxoedema, acromegaly, and Addisonism. Some very interesting facts have thus been discovered, which will, in due course, be fully described. All that need be said in this connexion at present is that there appears to be excessive energy along with increased frequency in Graves's disease; diminished electro-motive force, along with reduced frequency, in myxoedema; very variable conditions, according to its stage, in acromegaly; and, from first to last, remarkable loss of energy in Addisonism. There is a natural tendency to scepticism as regards the possibility of measuring the electro-motive force of the heart; but we shall assuredly, before long, be in a position to do so, as we can accurately estimate the resistance of the tissues and approximately the electro-motive energy generated by the cardiac pulsations. It will not be long before this is done in every case.

These affections, each in its own way so full of interest, have been chosen as the main theme of our discussion, for the reason that they furnish excellent opportunities for inquiry into the mode of operation of normal and morbid processes. The application of our new knowledge must now be attempted.

All organs—in fact, all tissues—receive from the blood certain substances, and yield in return others. Every function of the body, even a simple muscular contraction, furnishes material which is restored to the blood; much of this, however, is of the nature of waste. The glands produce special substances, to which alone the name of secretion can be properly applied. All of these glands are now assumed to yield an internal secretion; many, in addition, furnish also an external secretion. As an illustration, let me remark that the external secretion of the pancreas has for a long time been recognized as one of the most potent factors in the primary digestion, but it is only recently that the conception has arisen of internal secretion by the same gland—an internal secretion which is absolutely essential for the maintenance of carbo-hydrate metabolism.

The production of prosecretin by the intestinal mucous glands, discovered by Bayliss and Starling, a substance which, in the presence of acid becomes secretin, and stimulates the flow, both of the pancreatic and biliary secretions, has been the first step in our knowledge of a new chapter of physiological chemistry. Secretin is obviously a substance endowed with the power of influencing tissues and organs other than those from which it is itself derived. As a stimulant or excitant it has received from Starling the name of "hormone." Many glands in the body have the power of producing hormones, and year by year our knowledge of the subject is becoming more extensive and more thorough. Amongst these organs three are intimately concerned with the circulation, and to them let me (even at the risk of being tedious) for a few minutes call your attention.

The thyroid gland has, since the time of Schiff, been recognized to be closely associated with the nutrition of the body. It has been known from experiment that removal of the thyroid gland, and, by clinical observation, that its atrophy, result in conditions strictly analogous; and Schiff, Murray, and other observers have shown that the results of removal could be obviated by grafting portions of the gland. The further discovery that administration, whether by skin or mouth, of thyroid gland or any of its preparations brings about recovery from such affections, has proved the effect of the gland to lie in the production of an internal secretion, as was undoubtedly upheld by Schiff. As the result of a series of experiments on feeding with thyroid, Fordyce is inclined to believe the effect of large doses to be partial inactivity of the gland, which seems to confirm the observations of Carlson, Jacobson, Thompson, Marine, and Leuhart.

The internal secretion of the suprarenal capsules has been more recently discovered. Oliver and Schäfer found that extracts of the suprarenal bodies produced extreme contraction of blood vessels, even in very small doses. The administration of a small amount of suprarenal extract injected into the blood vessels is followed by the production of a rise of arterial pressure, due especially to constriction of the arterioles. The effect is sometimes obscured by stimulation of the cardio-inhibitory centre in the medulla, leading the heart to beat less frequently by impulses passing down the inhibitory nerves. If the vagi have been previously cut, or their action suspended by atropine, the rise of blood pressure may be very great. The effect of such a dose lasts only a few minutes; it may, however, be repeated over and over again. It has been found that the effect is brought about directly by the action of the drug on the muscular tissue of the heart and arteries. There is also stimulation of unstriped muscular fibres in many different situations—the intestinal, vesical, and uterine, as well as of the dilator of the pupil, and of the muscles of the hairs, and of certain glands, for example, the submaxillary. In fact, the results of suprarenal injection closely resemble stimulation of the sympathetic nervous system. But it has been proved that the active substance does not exert its influence upon the sympathetic nervous system itself, but only on the tissues to which the sympathetic nerves are distributed; it produces equally strong effects if these tissues are previously deprived of their sympathetic supply. It is interesting in this connexion to recall that the cells of the suprarenal medulla are developed in the embryo from tissue common to the sympathetic ganglia and to themselves.

In addition to its action upon the arterioles, suprarenal extract increases the tone of the muscular system in general. In excessive doses it produces deleterious results—marked acceleration and augmentation of the heart beat, frequent and shallow respiration, fall of temperature, paralysis of the limbs, especially the posterior extremities, glycosuria, and eventually cessation of respiration—such are the effects of overdoses.

For many years the pituitary body has occupied much of my attention, especially in regard to acromegaly and its congeners. The structure of the gland has been particularly studied by Andriezen and Herring. The earliest investigations to ascertain whether the pituitary body has any active functions were those of Oliver and Schäfer. They found that aqueous or saline extracts, which did not lose their activity even on boiling, produced rise of arterial pressure by effects upon the peripheral arteries, which are caused to contract strongly. They did not find any marked effect upon the rate of the heart, and they did not observe any difference in action by the different parts of the gland. Howell discovered that the anterior part of the gland has no physiological effect when injected into a vein, while the posterior produced the effects on the vessels described by Oliver and Schäfer. Howell further observed diminution of the rate of pulsation, and found that if a second dose be administered within a certain time after the first the effects are not repeated. Schäfer and Swale Vincent repeated Howell's observations, confirming them in almost every particular, but finding that the diminished frequency of the heart is not constant. Schäfer and Magnus shortly afterwards noticed as one of the results of intravenous injection a marked diuresis. Schäfer further, in association with Herring, discovered that an aqueous extract of the posterior part, including the pars intermedia, has a specific action both upon the vessels and cells of the kidney.

Herring showed that the anterior lobe of the pituitary body has the structure of a gland secreting into blood vessels, and that the posterior is composed of nervous tissue, surrounded and invaded by epithelial cells of the pars intermedia. He stated that this posterior lobe may furnish secretion into blood vessels, but holds that its arrangement and structure suggest a gland pouring its products into the infundibulum, and thence into the ventricles of the brain. He found that extracts of the anterior lobe have no immediate physiological action when injected into blood vessels; that extracts of the posterior lobe of birds and teleostean fishes have an action similar to those in mammals—that is, rise of pressure, expansion of kidney, and diuresis. Herring further set to work to discover the relation between the substance in the pituitary body and the colloid material of the thyroid gland which resembles it. He found that thyroidectomy produced no effect on the anterior lobe of the pituitary gland; but that, in the nervous part of the posterior lobe, and in the laminae forming the floor of the third ventricle, glandular, hyaline, and colloid bodies become very numerous. The significance of these changes is, as yet, unknown.

Halliburton, Candler, and Sikes fully confirmed the observations of Herring as regards the functions of the pituitary body, and were of opinion that the substances in the posterior lobe responsible for the effects are two in number—one pressor, and the other diuretic. As regards vicarious relationship between thyroid and pituitary, they carefully sought for iodine in the latter organ, with negative results. Simpson and Hunter have also attempted to investigate the possible vicarious relationship between the pituitary and thyroid glands, and, so far as the presence of iodine is conclusive, they discovered no trace of iodine in a large number of pituitary bodies, after thyroidectomy.

Argyll Campbell studied the effects of suprarenal and pituitary extract on the blood vessels. He found that suprarenal extract causes marked constriction of all the organs, with the exception of those of the heart and lungs. In the heart it produced slight constriction, and this was more evident in the case of the lungs. Pituitary extract contains at least two substances—one causing contraction, and the other relaxation. Each is capable of producing its characteristic effect on all the arteries, except the renal, where contraction is hardly ever obtained, the result being almost always relaxation.

The functions of the pituitary body formed the subject of the Croonian Lecture of the Royal Society, delivered three years ago by Schäfer, in which, after reviewing the various facts which have been mentioned, he described the effects of extirpation—the result of which, up to the date of the lecture, was uniformly death within forty-eight hours. Death was not the direct result of the operation, but was caused apparently by the loss of pituitary secretion. Paulesco, as well as Reford and Cushing, have performed a large number of experiments of this kind. As the result of a long series of feeding operations, Schäfer discovered that the use of the anterior lobe favours growth, and apparently the fact of grafting pituitary bodies is similar. He summed up the actions of the pituitary body as follows:

The pituitary body consists of three parts: (1) Anterior, formed of vascular glandular epithelium; (2) intermediate, formed of a less vascular epithelium secreting "colloid"; (3) posterior, consisting mainly of neuroglia, but invaded by the colloid, which passes through it into the infundibulum of the third ventricle. These parts differ from one another in function.

The function of the anterior part is probably related to growth of the skeletal tissues, including cartilage, bone, and connective tissue in general. The chief evidence in favour of this is derived from the fact that hypertrophy of the anterior part is associated with overgrowth of the skeleton and of the connective tissue in growing individuals, and of the connective tissues especially in individuals in whom growth has ceased.

The function of the intermediate part is to produce a "colloid" material which contains active principles or hormones acting upon the heart, blood vessels, and kidneys. Probably there are several such hormones acting upon blood vessels and kidneys independently, and also acting antagonistically, so that, according to circumstances, either a rise or fall of blood pressure, an increased or diminished secretion of urine, may be produced, and the effects on the kidney may be independent of those on the blood vessels. The hormones which appear to be most active are those which produce contraction of the blood vessels in general, with dilatation of the renal vessels and increased activity of renal cells, but there appear to be others which cause constriction of renal vessels and diminished activity of renal cells: the effects of these latter are generally less lasting. There is also usually an inhibitory effect produced on the heart.

Herring showed that in the elasmobranch fishes the secretion is poured directly into the blood vessels. There is no evidence of any direct secretion by the pituitary body into the brain ventricles. This is a most interesting fact, contrasting with the state of matters in the teleosteans.

In a further communication, Simpson and Hunter discovered that complete removal of the thyroid gland does not, even after five or six months, lead to the appearance of iodine in the pituitary body; this does not support the Rogowitsch theory, that in thyroid insufficiency the pituitary vicariously takes on its function.

In studying certain aspects of the mystery of life we are struck by an apparent lack of uniformity in the economy of Nature. At times there is a lavishness of structure and of function which to our present knowledge appears to be almost wasteful. This cannot be better exemplified than in the abundant profusion afforded by the essential reproductive processes of every living being, whether vegetable or animal. On the other hand, Nature appears to work in many directions by methods which indicate a distinct parsimony. This was well shown by Rolleston, who, in his Oxford Address, when applying Newton's statement: " Natura nihil agit frustra; et frustra fit per plura quod fieri potest per pauciora. Natura enim simplex est, et rerum causis superfluis non luxuriat"—pointed out that a law of parsimony may be found in many structures of the body. " She is prodigal in the variety of her adaptations. She is niggard in the invention of new structures." Rolleston suggested that where an organ can be diverted from one purpose and put to discharge another function, Nature will spare herself the expense of forming a new organ, and will adapt the old one to a new use; where she can employ a lowly organized structure, such as elastic tissue, she will spare herself the manufacture of a highly organized structure, such as muscle; where she can utilize matter that would otherwise be wholly refuse, Nature exemplifies this law by turning waste substances to useful account. In our study of glandular processes we find Nature lavish in her general provision, but parsimonious in particular instances at times.

Some of the changes in glandular activity, resulting in excess or defect of secretion, may be caused by processes which, in the light of our present knowledge, appear to be idiopathic; alterations brought about by particular diseases are much more easy to grasp, and a new chapter in pathology has recently been opened by certain discoveries regarding the effects of acute diseases on glandular tissue. Dubois showed that, after inoculations with cultures of diphtheria and other diseases, marked changes were found in the suprarenal glands. Langlois found, after diphtheria inoculation, that the suprarenal glands were hyperaemic, with diminution of the pressor action. Luksch ascertained, after injection of diphtheria cultures, that the pressor action of extracts from the suprarenal glands was wholly, or almost wholly, absent. Elliot discovered that exhaustion of the suprarenal glands is demonstrated by absence of the yellow staining action with bichromate salts, which was found within thirty-six hours of diphtheria poisoning. Humphrey Rolleston suggested the employment of adrenalin to prevent heart failure in diphtheria, and Meyer also advocated its use in this disease.

James Ritchie and Ninian Bruce have found that many of the sudden deaths which occur in diphtheria and other acute infections are produced by profound changes in the suprarenal glands. After death from the experimental production of diphtheria by inoculation, there is great swelling and hyperaemia of the suprarenal glands, and the medullary portion becomes completely exhausted of adrenalin. The exhaustion is complete in the less acute cases, while in the more acute there is very great diminution in the amount of adrenalin, from a condition of relative suprarenal inadequacy. The presence or absence of adrenalin is easily shown by placing the fresh glands in a solution of potassium bichromate and formalin. If the medullary cells take on a yellow stain, they contain adrenalin; they do not stain at all if adrenalin is absent. No other tissue in the body stains in this way, and the structures which thus react are appropriately termed "chromaffine cells" on account of this peculiar property. This exhaustion of the suprarenal glands is not specific for diphtheria toxaemia; it can also be produced by pneumococcal, streptococcal, staphylococcal, and other toxaemia. It may even be produced by any condition which throws prolonged strain upon the suprarenal gland.

In the lower vertebrates the cortex and medulla of the suprarenal bodies are separate organs. In birds they are irregularly mingled; in mammals alone does the cortex surround the medulla. The origin of the cortex and the medulla is of real import. The development of the medulla is very interesting and important. A very good description of this was furnished by Kohn. At an early stage small masses of cells are to be found on each side of the vertebral column. These cells are all identical. As they increase in size they suddenly divide into two different types. The one type grows slowly and develops into the ganglion cells of the sympathetic ganglia; the other develops more quickly, and shows the yellow staining reaction with bichromate solutions—that is, it assumes the character of "chromaffine tissue cells." The chromaffine cells and the sympathetic ganglion cells may thus be regarded as twins. The greater mass of these chromaffine cells atrophy after birth, but a few remain (1) in the midst of the sympathetic ganglia; (2) as separate masses, the accessory suprarenal bodies; (3) the largest mass remains and forms the medulla of the suprarenal glands; those in the cervical region form a small glandular mass known as the "carotid body." This manner of development is of profound significance in the relations of the suprarenal body and the sympathetic system. In a forthcoming work by Ninian Bruce, from which he has allowed me to quote, many of these interesting points will be found fully described.

There can be no doubt that the effects produced upon the nutrition of the tissues must be through the intervention of the blood vessels, but the further question arises, Is this influence exerted indirectly through nerves, or directly through chemical agencies? We know that the cervical, stellate, superior and inferior mesenteric ganglia may all be removed without death, and it is therefore clear that the tone of the cardio-vascular system does not necessarily depend upon an intact connexion with the sympathetic nervous system. This is universally admitted, and it must be regarded as the basis of all discussions connected with the relationship of the nervous, glandular, and circulatory apparatus. On the other hand, removal of the suprarenal glands proves fatal in twenty-four hours, and it is perfectly clear that, while life is not incompatible with destruction of much of the nervous control of the circulation, the removal of the structures which produce the chemical pressor substance is not compatible with life. We therefore believe the tone of the cardio-vascular mechanism to be influenced by two factors—nervous and chemical. Removal of the nervous factor is not fatal; removal of the chemical is. We are thus able to realize the full significance of exhaustion of the suprarenal glands in diphtheria, and can see how acute heart failure must be the consequence.

The whole subject of glandular affections is rendered still more complex by certain cases in which they are associated together or pass one into another. Such an instance is to be found in the interesting patient described by Murray, labouring at once under acromegaly and exophthalmic goitre; an almost equally interesting case of my own, in which acromegaly was accompanied by myxoedematous features, belongs to the same category; other combinations of similar nature have been recorded and somewhat complicate the whole matter. We now know that it is not uncommon to find Graves's disease ending in myxoedema; this is comparatively easy to explain, since the increased functional activity of the thyroid gland leads in time to loss of function.

Such reflections bring us back to the point from which we started. Are we yet in a position to decide whether the messengers which carry the impulses to the vessels and the tissues are nervous or chemical? We have seen that certain vascular processes are only possible when the vasomotor nerves are intact, but this is qualified by the further fact referred to—that destruction of the great sympathetic ganglia does not of necessity involve complete loss of vascular tone. As the outcome of certain experiments, we know that the action of hormones is direct. Kenneth Mackenzie has proved that the well-marked galactagogue action obtained from the posterior lobe of the pituitary body, and a few other structures, is by means of the direct effect of hormones upon the mammary gland. That it is not through the direct influence of the nervous system is quite clear, and that the nervous influence upon mammary secretion, which is well recognized, is probably an indirect one, operating, not upon the gland through its nerves, but upon the organs which supply stimulants to the blood, is most probable.

The recent investigations of Ascoli and Legnani are of profound interest. These observers removed the pituitary gland from young puppies. In each case two puppies of the same size (as nearly as possible) were selected—one for experiment, the other for control. In many cases the puppies operated on died two or three days afterwards ; but, in the few that survived, the results were remarkable. No further growth took place ; the puppy remained a puppy. The size of the body, of the head, of the limbs, remained as at the time of the operation. Ossification and dentition were arrested ; the bone not only ceased to grow, but showed defective nutrition ; while the nourishment of the whole organism suffered, and the animal only gained in fat. Reproductive development was completely arrested, and changes were seen in the spleen, the thymus, the thyroid, and the suprarenals.

Our understanding of the functions of the pituitary gland have been further extended recently by an interesting observation by Rennie, who describes a case of infantilism which was under his observation during three years, and in which it was found that an endothelioma had invaded the pituitary body, destroying the gland, so that very little of its proper structure remained. The patient was sixteen years old—quite undeveloped, with effeminate voice and other features of infantilism. The arterial pressure seemed high, and there was some polyuria, with headache and vomiting. The diagnosis was of a chronic interstitial nephritis. Harvey Cushing has recorded cases of tumour compressing the pituitary gland, in which the symptoms were mainly renal, and chronic interstitial nephritis was suspected.

We have to admit that there are other possibilities of structural or functional alterations through the influence of chemical processes without the intervention of glandular activities. We are forced to allow such possibilities by the consideration that many glandular changes occur without apparent alteration of structure or function elsewhere. As an example of this let me mention that there are pituitary enlargements without acromegaly. Modifications in viscosity and alterations in osmosis cannot be neglected. It is indeed quite possible that growth is conditioned by the inherent tendencies of the part, and regulated by the special activities of the cells. Some of them become too large in size for the nourishment of their central protoplasm, and therefore it undergoes necrotic changes. Various perversions of ossification prove this. Again, the supply of nourishment for the cell may be deficient in quantity or poor in quality ; while, again, it may be too great in amount or too rich in character. On the other hand, there may be divergences from the normal processes of removal, elimination being too active or too sluggish. As yet we know but little of the effects of such changes, yet they have been recognized through histological investigation. The consideration of this subject has led Geddes to believe that many of the changes found in the long series, beginning with achondroplasia at the one end and terminating in gigantism at the other, are brought about by alterations in the nitrogen content of the blood—probably arising from hepatic eccentricities. He has been led to think that the enlargement of the pituitary body in acromegaly is probably to be regarded as a protective process whereby there is an attempt to regulate the disturbances of the tissue changes.

Simple arrest of development, whether antenatal or postnatal, may be sufficient to produce dwarfism; and, on the other hand, accelerated development may in both phases of existence be the first impetus towards gigantism. Whether such effects are due to an inherent tendency implanted on the tissues, directly or indirectly through the glandular or nervous system, no man can yet say.

At any period of life normal growth and decline may be interfered with by agencies either from without or from within. Alterations in the amount of nutriment; changes in powers of assimilation and elimination; the effects of microbes and toxins—all of these require our most careful consideration. The relative importance to be attributed to the different factors in maintaining the equilibration of the tissue processes is necessarily a subject still in its infancy, but none the less meriting our thoughts.

The most interesting facts ascertained some years ago by Dixon as to the effects upon the circulation of extracts from the heart muscle in various conditions of rest and fatigue show how very powerful are the chemical influences at work in the regulation of function.

When we consider some of the arrangements by which the sympathetic system is linked up with the cerebrospinal axis we can understand how profoundly the central nervous system may be affected by impulses from the periphery and how reciprocal influences are exerted. Let me mention that the grey rami communicantes appear from experimental work to be composed of fibres which take their origin in the vertebral ganglia of the sympathetic, and that these rami probably carry vasomotor impulses to the blood vessels of the cord; we can grasp the profound significance of the connexion. The fibres of the grey rami seem, indeed, to be relay fibres on the outgoing vasomotor path, recurving backwards and carrying impulses to the vascular supply of the central nervous system. They are, therefore, recurrent, like the fibres described by Magendie as re-curving and re-entering the cord with the anterior roots in order to supply the membranes of the cord with sensibility. Langley and Sherrington consider the fibres of the grey rami entirely postganglionic—that is, efferent from sympathetic ganglia, but intended for distribution to the cord vessels.

A paper of the greatest interest, by Elliott, appeared last week. Elliott has found that profound nervous influences, such as fright, produce very definite changes in suprarenal secretion. He is led to believe that the suprarenal glands are played upon by the splanchnic nerves in emotional reflexes with delicate adjustment.

Possibly some of my hearers may be inclined to regard the subject of these remarks as purely academic, and of no practical importance in the world of clinical medicine. There could not be a greater mistake. Every observation that has been cited to-day is of the highest value in the treatment of disease; and although our therapeutic measures are still characterized by unavoidable crudeness of means, there can be no doubt that the views of to-day are much more characterized by singleness of aim and simplicity of method than in any previous epoch of the world's history. It is probable that the art of therapeutics will remain for long one of the most difficult branches of scientific investigation. It is complicated by so many cross currents that absolute certainty is difficult of attainment. Many of our views depend on apparent analogies and indirect arguments. Let us for one moment look at the question of the action of drugs on vessels. Can we be certain that they act on muscle fibres directly, or through nerve endings indirectly? Adrenalin is believed to act on nerve endings, because it only, or mainly, causes contraction of vessels with sympathetic innervation, because it acts almost everywhere else where there are sympathetic nerve ends, and because it no longer contracts vessels after large amounts of ergotoxin, while stimulation of the vasomotor constrictor nerves loses effect at the same time. Digitalis, again, is held to act on muscle because it contracts muscles quite irrespective of the character of the nerves going to them, because it acts on many forms of muscle in large doses, and because it continues to contract vessels after ergotoxin has been given in quantities sufficient to prevent any adrenalin action, or any effect from stimulation of the vaso-constrictor nerves. These questions involve what is, after all, simply a balance of probabilities, as is so clearly stated by Cushny.

The employment of thyroid extract in myxoedema is, thanks to the work of Mackenzie, Murray, and many of their successors, so thoroughly established as to require no remark. The influence of this potent substance upon the nutrition of the body must be explained by its action as a hormone. Whether it acts directly upon glands and tissues, or indirectly through the intervention of the nervous system, cannot at present be determined. Suffice it to say that it influences blood distribution and nutritive possibilities in the most powerful manner. From the practical point of view, you will perhaps permit me, while passing by its obvious uses in clear cases of myxoedema and cretinism, to mention the invaluable service which may be obtained from thyroid extract in several conditions which are apt to miss our attention. Minor degrees of thyroid inadequacy are found about the climacteric period, or shortly afterwards. They are often mistaken for cardiac troubles, as they are attended in many instances by breathlessness and palpitation, bradycardia, and (less frequently) tachycardia. Such symptoms, along with slight increase in bulk, are misleading. It has been my fortune to see very many patients answering to this description, and to find that, by the employment of extremely small doses of thyroid extract, complete disappearance of all the disturbances was attained.

In youth, again, it is common to find lack of growth in both sexes. Occasionally we find children, and, still more, youths, stunted in growth, but excellent in form. One such will never, so long as memory lasts, leave the upper surface of my cerebral palimpsest. The son of one of my medical friends was, in his 18th year, 1 in. below 5 ft. in height. He had set his whole mind upon entering Woolwich, for which his one and only chance was just about six months ahead. The family turned to me in deep distress, as they felt that to obtain a growth of 4 in. in six months would be as great a feat as the addition of the proverbial cubit to the stature. By the employment of thyroid extract the youth grew 7 in. in six months, and, as he obtained one of the highest places in the entrance examination for Woolwich, it was obvious that his cerebral functions had been in nowise disturbed by the treatment. Several instances of the same sort—not, however, quite so dramatic—have been under my care; to be quite frank, it must, nevertheless, be confessed that, in some of these boys and girls, even thyroid treatment absolutely fails to produce the desired effect.

Another class of patient in whom we find thyroid extract invaluable consists in children and youths who manifest mild myxoedematous features—they are not for a moment, however, to be regarded as cretinoid. In many of those young people, along with satisfactory growth as regards height, there is rather too much corporeal bulk and rather too little cerebral energy. Under thyroid treatment they become more slender and the sluggishness of the intellectual processes entirely disappears. How these different conditions of hypothyroidism are brought about is often a complete mystery. The infections are in some cases responsible.

Ever since the observations of Oliver and Schäfer upon the suprarenal glands, their substance has been employed by me as the most important remedy in the treatment of Graves's disease. Various mineral and vegetable substances have, in the past, been administered freely in this disease, and in more recent times the blood of dethyroidized goats has been largely used. This latter substance has in my hands, as in those of Murray, proved to be of about the same value as the *pulvis Olympicus* poured upon us by a racing car on a summer day. But in suprarenal extract we have an agent which may be stated fearlessly to have no rival in the management of this affection. Under its employment the rate of the pulse is reduced, the protrusion of the eyeballs disappears, the thyroid gland diminishes, the tremor, along with every other nervous symptom, vanishes, and the patient is restored to health in a way that we never see under any other method of treatment. No one who knows me will accuse me of aught but the most sympathetic attitude towards modern surgery; but this is one of the affections in which it is my duty solemnly to protest against the *furor operativus* which, in this condition, is in the overwhelming proportion of cases absolutely unjustifiable. It is surely far more scientific, as it is certainly much more successful, to trust to the chemical messenger, or hormone, which has the power of regulating the glandular activity responsible for so much of the clinical picture in Graves's disease, than to risk doubtful surgical adventures.

As to the treatment of acromegaly, we are still on the threshold of inquiry. In some early cases the use of pituitary substance has, in my own hands, been remarkably beneficial; even in later stages, although the effects have not been so striking, much relief has been obtained from a number of the subjective symptoms, while the general condition has been kept stationary. There are, however, many cases—and these are especially of the myxoedematous type already mentioned—in which the employment of thyroid substance furnishes the only means of amelioration. In those instances in which there are features suggestive of a concurrent Graves's disease, suprarenal substance (sometimes along with pituitary gland) is of real use. The action of the pituitary substance upon the blood vessels has, by the way, since the researches of Oliver and Schäfer, helped us enormously in the treatment of certain conditions where the arterial pressure has a tendency to fall. In many instances of pneumonia and other acute diseases, apt to be accompanied by fatal fall of arterial pressure, the hormone obtained from the posterior lobe of the pituitary gland is of the greatest use.

Did time permit, it would be a matter of the highest interest to point out that, during the menopause, many—sometimes all—of the troublesome symptoms then experienced may be removed, or at least relieved, by ovarian substance, while analogous effects are obtained during the corresponding period in men by didymin.

The new conceptions of Addison's disease have, as has been already shown, greatly widened our knowledge of suprarenal functions. We recognize that, as the result of many factors, the suprarenal bodies may be deficient in function. It is certain that pyrexia, from the most varied causes, can abrogate the functions of these glands and bring about even fatal diminution of arterial pressure. In many of these conditions, thanks to the labours of those who have been specially referred to, we now recognize that the use of suprarenal substance, or of adrenalin, will bring about recovery, through supplying the necessary hormone, until the glands are able to resume their functions. In a very large number of affections, therefore, it is absolutely necessary to have recourse to such modern methods of treatment.

Of an excess of suprarenal secretion, we at present know little or nothing; but a suspicion, first publicly voiced by

Russell, that over-action of the suprarenal bodies may be responsible for certain cases of arterial degeneration must be referred to, and, as the treatment of such cases by means of thyroid substance—largely antagonistic to suprarenal secretion—has been followed by excellent results, the suggestion appears to be well founded. The experimental production of arterial degeneration in rabbits by adrenalin is a matter requiring further research.

We sometimes speak of pharmacological diagnosis, meaning thereby that, knowing certain diseases to be amenable to particular remedies, we believe that our provisional conclusions are correct if the affections yield to the methods. But the therapeutic touchstone is sometimes misleading, inasmuch as our remedies produce effects over a much wider area than we may be inclined to dream of. This in itself shows the uncertainty attending our pharmacological investigations. When we further consider that the agents we employ may act directly or indirectly, we are led to admit that we are only, after all, dealing with fragmentary knowledge or "broken lights."

We have to put to ourselves the important question, How do these powerful agents produce the changes we have traced? We have seen that they act upon many, perhaps all, tissues. Some probably act on the local processes of renewal and removal, and others by their effects on the muscular wall of the vessels; certain undoubtedly act on the tissues, not directly or even by modifying the vessels, but through the sympathetic system. It seems probable that they invoke nervous influences, consisting in waves of molecular disturbance, which bring about changes by liberation or inhibition. The recent work of Elliott, previously referred to, supports this view.

The results of these interesting advances must enhance our hopes of even more valuable additions to our knowledge, theoretical and practical, at a date not far distant. Their consideration opens a vista of infinite possibilities in the explanation of normal functions, the comprehension of morbid processes, and the management of diseased conditions. We are still groping after solid facts in the dusky twilight of the dawn, but we doubt not that the brighter radiance of the day will reveal much that is now hidden from our eyes. All that we can now know, all that we can now do, is the result of modern methods of investigation. Led by the whole trend of our education to set a high value on all honest work that explains the scientific problems and assists the practical treatment of disease, the results obtained by devotion to the three sister studies —physiology, pathology, and pharmacology—are to us of paramount importance. It is not given to us all in equal measure to contribute to the advance of knowledge; we, as clinicians, gladly avail ourselves of the labours of those devoted men who illuminate many vexed questions by their experimental researches.

We are like children on a beach of shifting sands; successive tides mould the form of the shore, gradually washing away, but as steadily building up, the coast of the future. So it is with ourselves; with the constant movement of thought, and the alternate advance and retreat of opinion, there are incessant changes. Contemplating these fluctuations, we are sometimes inclined to be impatient, and to wonder whether, after all, there is a real constructive movement.

But science, ever young, looks with the open eyes of Hope and Faith into the future; and those of us who can possess our souls in patience, trusting her methods, feel the assurance of greater conquests ere long. Recognizing that we live in an age of magnificent achievement, we shall be able, if there be any tendency to disappointment, to say:

> "Shall we not take the ebb, who had the flow?"

For some of us, the curfew of life will soon quiver upon the evening air. It is of the very essence of our being to experience a sense of unfulfilment; to feel that we have, at least in some degree, been unprofitable servants. But, if we have been faithful to our beliefs, and steadfast in our labours, we shall escape the bitter regret of wasted hours and unused opportunities, and we shall enjoy the satisfaction of knowing that, to the best of our powers, we have attempted to extend the knowledge, and increase the welfare, of mankind. Even if we may not witness, in our own time, the ends for which we have struggled, we shall have the consoling prospect that our successors will behold what we have longed to see. In the meantime, let us, in all our doings, walk along the path of safety, through accurate observation, and unprejudiced investigation, wielding fearlessly the spear of Ithuriel in defence of eternal truth.